Express Mail Label No. EL 622 831 899 US 11-14-00 A

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No. 287985/002
Total Pages in this Submission

TO THE ASSISTANT COMMISSIONER FOR PATENTS
Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

TREATMENT OF PARKINSON'S DISEASE

and invented by:

If a CONTINUATION APPLICATION, *check appropriate box and supply the requisite information:*

☐ **Continuation** ☒ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: 09/287,951

Which is a:

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: _____

Which is a:

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: _____

Enclosed are:

Application Elements

1. ☐ Filing fee as calculated and transmitted as described below
2. ☒ Specification having 13 pages and including the following:
   - a. ☒ Descriptive Title of the Invention
   - b. ☐ Cross References to Related Applications *(if applicable)*
   - c. ☐ Statement Regarding Federally-sponsored Research/Development *(if applicable)*
   - d. ☐ Reference to Microfiche Appendix *(if applicable)*
   - e. ☒ Background of the Invention
   - f. ☒ Brief Summary of the Invention
   - g. ☒ Brief Description of the Drawings *(if drawings filed)*
   - h. ☒ Detailed Description
   - i. ☒ Claim(s) as Classified Below
   - j. ☒ Abstract of the Disclosure

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No. 287985/002
Total Pages in this Submission

Application Elements (Continued)

3. ☒ Drawing(s) *(when necessary as prescribed by 35 USC 113)*

   a. ☒ Formal b. ☐ Informal Number of Sheets 2

4. ☒ Oath or Declaration

   a. ☐ Newly executed *(original or copy)* ☐ Unexecuted

   b. ☒ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*

   c. ☒ With Power of Attorney ☐ Without Power of Attorney

   d. ☐ *DELETION OF INVENTOR(S)*
   Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. 1.63(d)(2) and 1.33(b).

5. ☐ Incorporation By Reference *(usable if Box 4b is checked)*
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. ☐ Computer Program in Microfiche

7. ☐ Genetic Sequence Submission *(if applicable, all must be included)*

   a. ☐ Paper Copy

   b. ☐ Computer Readable Copy

   c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☐ Assignment Papers *(cover sheet & documents)*

9. ☐ 37 CFR 3.73(b) Statement *(when there is an assignee)*

10. ☐ English Translation Document *(if applicable)*

11. ☐ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations

12. ☐ Preliminary Amendment

13. ☐ Acknowledgment postcard

14. ☒ Certificate of Mailing

    ☐ First Class ☒ Express Mail *(Specify Label No.):* EL 622 831 899 US

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No. 287985/002
Total Pages in this Submission

Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*

16. ☐ Small Entity Statement(s) - Specify Number of Statements Submitted: _____

17. ☐ Additional Enclosures *(please identify below):*

Request That Application Not Be Published Pursuant To 35 U.S.C. 122(b)(2)

18. ☐ Pursuant to 35 U.S.C. 122(b)(2), Applicant hereby requests that this patent application not be published pursuant to 35 U.S.C. 122(b)(1). Applicant hereby certifies that the invention disclosed in this application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication of applications 18 months after filing of the application.

Warning

An applicant who makes a request not to publish, but who subsequently files in a foreign country or under a multilateral international agreement specified in 35 U.S.C. 122(b)(2)(B)(i), must notify the Director of such filing not later than 45 days after the date of the filing of such foreign or international application. A failure of the applicant to provide such notice within the prescribed period shall result in the application being regarded as abandoned, unless it is shown to the satisfaction of the Director that the delay in submitting the notice was unintentional.

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No. 287985/002
Total Pages in this Submission

Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra	Rate	Fee
Total Claims	21	- 20 =	1	x $9.00	$9.00
Indep. Claims	3	- 3 =	0	x $40.00	$0.00
Multiple Dependent Claims (check if applicable) ☐					$0.00
				BASIC FEE	$355.00
OTHER FEE *(specify purpose)* _____					$0.00
				TOTAL FILING FEE	$364.00

☐ A check in the amount of to cover the filing fee is enclosed.

☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. **19-4709** as described below. A duplicate copy of this sheet is enclosed.

- ☒ Charge the amount of **$364.00** as filing fee.
- ☒ Credit any overpayment.
- ☒ Charge any additional filing fees required under 37 C.F.R. 1.16 and 1.17.
- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

Dated: 11-13-00

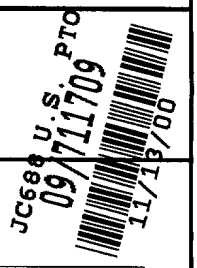
Signature

Steven B. Pokotilow
Reg. No. 26,405
STROOCK & STROOCK & LAVAN LLP
180 Maiden Lane
New York, New York 10038

cc:

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): **Moshe Kushnir et al.**			Docket No. **287985/002**
Serial No. **New Application**	Filing Date **Herewith**	Examiner	Group Art Unit

Invention: **TREATMENT OF PARKINSON'S DISEASE**



I hereby certify that the following correspondence:

Utility Patent Application Transmittal; specification (13 pages); copy of prior Declaration and Power of Attorney and 2 sheets of formal drawings

(Identify type of correspondence)

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Assistant Commissioner for Patents, Washington, D.C. 20231 on

11/13/00
(Date)

Patricia Driscoll
(Typed or Printed Name of Person Mailing Correspondence)

Patricia Driscoll
(Signature of Person Mailing Correspondence)

EL 622 831 899 US
("Express Mail" Mailing Label Number)

Note: Each paper must have its own certificate of mailing.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Moshe Kushnir and Eli Heldman

Filed : Concurrently herewith

For : New Divisional Application based on U.S. Patent Application Serial No. 09/287951 filed April 7, 1999 for TREATMENT OF PARKINSON'S DISEASE

Docket No. 287985/0002
BVO:lgs

November 13, 2000

PRELIMINARY AMENDMENT

Honorable Assistant Commissioner for Patents
Washington D.C. 20231

Sir:

Prior to examination of the above-referenced divisional application on its merits, please amend the above-referenced Application as follows:

IN THE TITLE:

Please change the title to -- **AN APPARATUS FOR THE TRANSDERMAL TREATMENT OF PARKINSON'S DISEASE** --

IN THE CLAIMS:

Please cancel claims 1-9 and 21, without prejudice.

"Express Mail" Mailing Label Number: EL622831899US
Date of Deposit: 11-13-00
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to: *Assistant Commissioner for Patents, Washington, D.C. 20231.*
Name: Patricia Driscoll

REMARKS

Applicants make this Amendment prior to examination in connection with the filing of a divisional application directed to claims restricted out of the parent and now allowed United States Patent Application Serial No. 09/287,951. Applicant submits that remaining claims 10-20, drawn to an apparatus for delivering a composition to treat Parkinson's Disease transdermally, are in condition for allowance.

The Claims 1-9 and 21 drawn to a composition for the treatment of Parkinson's disease were substantially examined and allowed by the Examiner in U.S. application Serial No. 09/287951. What is novel about the claimed apparatus is both its configuration and its intended use in conjunction with various formulations for the transdermal treatment of diseases, specifically Parkinson's disease. Accordingly, Applicants submit that claims 10-20 are in condition for allowance. If the Examiner is unable to issue an immediate Notice of Allowance, the Examiner is respectfully requested to telephone the undersigned attorney.

Respectfully submitted,

By: _____

Steven B. Pokotilow
Registration No. 26,405
Attorney for Applicant
STROOCK & STROOCK & LAVAN LLP
180 Maiden Lane
New York, New York 10038-4982
(212) 806-5400

APPLICATION OF

MOSHE KUSHNIR

AND

ELI HELDMAN

FOR LETTERS PATENT OF THE UNITED STATES

FOR IMPROVEMENTS IN

TREATMENT OF PARKINSON'S DISEASE

Rashida A. Karmali
Registration No. 43,705
Attorney for Applicants
Stroock & Stroock & Lavan LLP
180 Maiden Lane
New York, New York 10038
(212) 806-5400

Docket No. 287985/002

METHODS AND APPARATUS FOR TREATMENT OF PARKINSON'S DISEASE

FIELD OF THE INVENTION

The present invention relates to methods and apparatus for treatment of Parkinson's disease.

BACKGROUND OF THE INVENTION

Parkinson's disease (PD) is one of the most common neuro-degenerative diseases which affect the elderly.

The following is a representative list of references which discuss Parkinson's disease and therapeutic strategies:

1. de Rijk MC, Breteler MMB, Graveland GA, et al. Prevalence of Parkinson's disease in the elderly: The Rotterdam study. Neurol. 1995; 45:2143-2146.

2. Bennet DA, Beckett LA, Murray AM, et al. Prevalence of Parkinsonian signs and associated mortality in a community population of older people. N Engl. J. Med. 1996; 334(2):71-76.

3. Hornykiewicz O, Kish SJ. Biochemical pathophysiology of Parkinson's disease. Adv Neurol. 1986; 45:19-34.

4. Leenders KL, Salmon EP, Tyrrel P, et al. The nigrostriatal dopaminergic system assessed in vivo by positron emission tomography in healthy volunteer subjects and patients with Parkinson's disease. Arch Neurol. 1990; 47:1290-1298.

5. LeWitt PA. Levodopa Therapeutics: New treatment strategies. Neurology 1993; 43(suppl. 6):S31-S37.

6. Peppe A, Dambrosia JM, Chase TN. Risk factors for motor response complications in L-Dopa treated parkinsonian patients. Adv Neurol 1993; 60:698-702.

7. Chase TN, Mouradian MM, Engber TM. Motor response complications and the function of striatal efferent systems. Neurology 1993; 43(suppl. 6): S23-S27.

8. Doller HJ, Connor JD. Changes in neostriatal dopamine concentrations in response to levodopa infusions. J Neurochem 1980; 34:1264-1269.

9. Spencer SE, Wooten GF. Altered pharmacokinetics of L-dopa metabolism in rat striatum deprived of dopaminergic innervation. Neurology 1984; 34:1105-1108.

10. Spencer SE, Wooten GF. Pharmacologic effects of L-dopa are not closely linked temporally to striatal dopamine concentration. Neurology 1984; 34:1609-1611.

11. Hardie RJ, Malcolm SL, Lees AJ, et al. The pharmacokinetics of intravenous and oral levodopa in Parkinson's patients who exhibit on-off fluctuations Br J Clin Pharmacol 1986; 22:421-436.

12. Fabbrini G, Juncos J, Mouradian MM, et al. Levodopa pharmacokinetic mechanisms and motor fluctuations in Parkinson's disease. Ann Neurol 1987; 21:370-376.

13. Nutt JG, Woodward WR, Hammerstad JP, et al. The "on-off" phenomenon in Parkinson's disease: relation to levodopa absorption and transport. N Engl J Med 1984; 310:483-488.

14. Shoulson I, Glaubiger GA, Chase TN. On-off response: clinical and biochemical correlations during oral and intravenous levodopa administration in parkinsonian patients. Neurology 1975; 25:1144-1148.

15. Quinn N, Parkes JD, Marsden CD. Control of on/off phenomenon by continuous intravenous infusion of levodopa. Neurology 1984; 34:1131-1136.

16. Schuh LA, Bennet JP. Suppression of dyskinesias in advanced Parkinson's disease. I. Continuous intravenous levodopa shifts dose-response for production of dyskinesias but not for relief of parkinsonism in patients with advanced Parkinson's disease. Neurology 1993; 43:1545-1550.

17. Sage JI, McHale DM, Sonsulla P, et al. Continuous levodopa infusion to treat complex dystonia in Parkinson's disease. Neurology 1989; 39:888-891.

18. Schelosky L, Poewe W. Current strategies in the drug treatment of advanced Parkinson's disease - new modes of dopamine substitution. Acta neurol Scand 1993; 87(suppl. 146):46-49.

19. Nutt JG, Woodward WR. Levodopa pharmacokinetics and pharmacodynamics in fluctuating parkinsonian patients. Neurology 1986; 36:739-744.

20. Nelson MV, Berchou RC, LeWitt PA, et al. Pharmacodynamic modeling of concentration-effect relationship after controlled-release carbidopa/levodopa (Sinemet CR-4) in Parkinson's disease. Neurology 1990; 40:70-74.

21. Bredberg E, Nilson D, Johansson K, et al. Intraduodenal infusion of a water-based levodopa dispersion for optimisation of the therapeutic effect in sever Parkinson's disease. Eur J Clin Pharmacol 1993; 45:117-122.

22. Mouradian MM, Juncos JL, Fabbrini G, et al. Motor fluctuations in Parkinson's disease: central pathophysiological mechanisms. Part II. Ann Neurol 1988; 24;372-378.

23. Sage JI, Mark MH. The rationale for continuous dopaminergic stimulation in patients with Parkinson's disease. Neurology 1992; 42(Suppl. 1):23-28.

24. Chase TN, Baronti F, Fabbrini G, et al. Rational for continuous dopaminometic therapy of Parkinson's disease. Neurology 1989; 39(Suppl. 2):7-10.

25. Sage JI, Mark MH. Basic mechanisms of motor fluctuations. Neurology 1994; 44(Suppl. 6):S10-S14.

26. Sage JL, Trooskin S, Sonsalla PK, et al. Experience with continuous enteral levodopa infusions in the treatment of 9 patients with advanced Parkinson's disease. Neurology 1989; 39(Suppl. 2):60-63.

27. Mouradian MM, Heuser IJE, Baronti F, et al. Modification of central dopaminergic mechanisms by continuous levodopa therapy for advanced Parkinson's disease. Ann Neurol 1990; 27:18-23.

28. Bravi D, Mouradian MM, Roberts JW, et al. End-of-dose dystonia in Parkinson's disease. Neurology 1993; 43:2130-2131.

29. Tanner CM, Melamed E, Lees AJ. Managing motor fluctuations, dyskinesias and other adverse effects in Parkinson's disease. Neurology 1994; 44(Suppl. 1):S12-S16.

30. Joseph King Ching Tsui. Future Treatment of Parkinson's disease. Can J Neurol Science 1992; 19:160-162.

31. Djaldetti R, Atlas D, Melamed E. Subcutaneous injections of levodopa-ethylester: A potential novel rescue therapy for response fluctuations in patients with Parkinson's disease (Abst). Neurology 1995; 45(Suppl. 4):415S.

32. LeWitt PA. In: Levodopa controlled-release preparations. Neurology 1993; 43(Suppl. 6)S38-S40.

33. Koller WC, and Pahwa R. Treating motor fluctuations with controlled-release levodopa preparations. Neurology 1994; 44(Suppl. 6):S23-S28.

The prevalence of diagnosed PD in the population above the age of 55 is about 1.4% and it increases with age (Ref. 1). Moreover, Parkinsonian signs in the elderly are estimated to occur in 30% of the population over the age of 65 (Ref. 2). Although PD is considered a multisystem disease, it is mainly a movement disorder caused by a continuous, long lasting degeneration of the dopaminergic neurons that are located in the mesencephalic substantia nigra pars compacta. PD becomes symptomatic only after degeneration of about 60-80% of these dopaminergic neurons, or after the loss of about 90% of the striatal dopamine (Refs. 3, 4). Dopamine (DA), which is produced within the substantia nigra, reaches the

striatum via the nigro-striatal tract and is released at the striatal synapses. DA deficiency in the striatum, due to the degeneration of the dopaminergic neurons in the substantia nigra, is considered to be the cause of PD. Consequently, the most effective treatment of PD is Levodopa (LD), which is converted to DA by enzymatic decarboxylation. Inhibition of the peripheral aromatic amino acid decarboxylase by carbidopa (an inhibitor that cannot penetrate the blood-brain-barrier) improves dramatically the results of the treatment. However, the currently available LD preparations are effective only for a relatively short period and may be even deleterious, under certain conditions (as will be explained below).

Administration of LD is especially successful during early stages of the disease. Adverse effects of LD, such as dyskinesias and hallucinations that occur at early stages of the disease are dose-dependent. These adverse effects are attributed to hypersensitivity of denervated striatal dopaminergic receptors to exogenous dopamine (Ref. 5). At late stages of the disease additional types of adverse effects appear as the response to LD becomes unpredictable, fluctuative and the duration of the response is reduced. Motor fluctuations appear after about 4 - 5 years from the introduction of LD therapy in 24%-84% of the patients (Ref. 6). The most common and disabling motor complications are: 1) "wearing-off" fluctuations; 2) "on-off" fluctuations and 3) peak-dose dyskinesias (Ref. 7).

The "wearing-off" effect means a reduction in the duration of the beneficial effect after each administration of LD. During this period, LD must be administered more frequently than before, a problem which severely affects the quality of life of the patient. Complications such as "wearing off" may arise due to limitation of storage capacity of DA in the CNS (Refs. 5, 8-10). When neuronal DA storage is reduced, the clinical state of the patients becomes fully dependent on the fluctuating blood level of LD. Since the normal half-life of LD in the circulation is 1-2 hours (Refs. 11-13), LD should be administered at this stage more frequently and the effect is fluctuative. Moreover, with the currently available oral preparations, the blood level of LD is a function of the rate of absorption from the gastro-intestinal tract, which is irregular and uncontrollable. The resulting fluctuations of the LD blood levels contribute further to the instability of the effect. A continuous drug delivery, which maintains a constant blood level of LD, has been shown to improve significantly the clinical state of the fluctuating parkinsonian patients (Refs. 13-18). In this regard, it has been reported that therapeutic effects of LD were noticed when LD plasma levels reached 300-800 ng/ml (Refs. 19-21).

The "on-off" fluctuations are inconsistent transitions between a hypokinetic parkinsonian state (the "off" state) and a hyperkinetic state (the "on" state). The clinical state of these patients is highly correlated with the plasma concentration of LD (Refs. 5, 20). It is thought that these fluctuations result from a narrowing of the therapeutic window of LD. An intermittent administration of LD, given for a long period, is considered to be one of the major causes of the reduction of the therapeutic window (Refs. 22, 23) and consequently leads to the motor fluctuations (Refs. 23-25). On the other hand, a continuous infusion of LD has been shown to increase the therapeutic window and to reduce the "on-off" fluctuations (Refs. 25-27). Moreover, during a continuous administration, the blood levels of LD which are needed to keep the patient at the "on" state gradually decrease (Ref. 21).

Peak-dose dyskinesia is a common advanced motor complication which occurs when the blood level of LD rises to its peak. This complication is observed in advanced stages of the disease when patients show a very steep dose-response curve. Under such circumstances, small shifts in circulating LD levels, and thus in cerebral DA, induce major swings in the clinical state (Ref. 7). In this stage of the disease, a continuous administration that keeps the circulating LD level constant, may prevent the dyskinesias. Moreover, these kinds of dyskinesias, like the "on-off" dyskinesia, may not develop during a continuous administration of LD (Refs. 7, 16, 17, 28, 29).

All these findings and observations clearly suggest that a continuous delivery of LD is advantageous over an intermittent administration. Persistent attempts have been made in effort to develop a sustained delivery of LD (Refs. 30, 31). Strategies to improve the clinical results of intermittent LD administration include controlled release (CR) preparations and pump-delivery of LD. However, the existing preparations and devices suffer from several disadvantages as follows:

1. CR preparations have a delayed onset. The peak effect of Sinemet CR (commercially available from Merck Sharp and Dohme Research Laboratories) was shown to occur an hour later than that of the conventional Sinemet (Refs. 18, 32).

2. The bioavailability of the CR preparations is low (Refs. 18, 32). The low bioavailability is explained by the variable properties of the gastro-intestinal tracts (Ref. 33).

3. Reduced reliability and predictability of the clinical response (Refs. 32, 33).

4. According to many investigators, the CR preparations do not provide the same favorable effect which was demonstrated by a continuous administration of LD such as an IV infusion (e.g., Refs. 5, 15, 18).

5. Sclerosis of the peripheral veins occurs frequently during an IV infusion of LD (Ref. 5).

6. A gastrostom-duodenal tube or an esophageal catheter is very unpleasant.

To overcome these disadvantages, and yet to administer LD in a continuous manner, an alternative method of drug delivery is needed.

SUMMARY OF THE INVENTION

In the present invention, we claim that transdermal delivery of LD could be the best substitution for the methods of continuous invasive infusions, free of disadvantages of the currently available strategies.

The present invention constitutes a solution to most of the problems associated with the currently available treatments, and thus provides a safer and more effective treatment for PD.

The invention describes a novel route of administration of levodopa dissolved in a formulation which is designed to maintain stability of the drug in solution and enables continuous penetration of the drug through the skin. This method is suggested as a treatment of Parkinson's patients, especially at advanced stages of the disease. The currently available LD preparations cause side effects and deterioration in the clinical state of the disease. The present invention helps overcome these disadvantages.

In accordance with a preferred embodiment of the present invention, an alkyl-ester of LD such as levodopa-ethyl-ester (LDEE) is administered transdermally. For this purpose, the alkyl-ester of LD is dissolved in an appropriate formulation. The formulation consists of propylene glycol, a fatty acid and a detergent. The LD-alkyl-ester and the formulation (the solvent) are kept separately and mixed just before the beginning of the drug application. A transdermal device which includes a container connected to a patch via a narrow plastic tube is used for the transdermal delivery. The container is re-filled every 24 h. The patch is fed with the LD-alkyl-ester solution preferably by gravity, or alternatively by pump, the solution then being spread on the skin area covered by the patch. During treatment, the patient ingests tablets of carbidopa (25 - 50 mg/tablet) three times a day. According to the clinical needs, the patient could receive a supplemental treatment such as oral anti-parkinson's drug.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be understood and appreciated more fully from the following detailed description, taken in conjunction with the drawings in which:

Fig. 1 is a simplified pictorial illustration of apparatus for transdermal administration of levodopa, constructed and operative in accordance with a preferred embodiment of the present invention; and

Fig. 2 is a simplified sectional illustration of apparatus of Fig. 1, taken along the lines II - II in Fig. 1.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

A formulation (solvent) useful in transdermal treatment of Parkinson's disease, in accordance with a preferred embodiment of the present invention, is now described.

The formulation is designed to dissolve a treating drug (alkyl-ester of LD) and maintain it stable in solution for the period during which a continuous transdermal penetration takes place. Preferably, the formulation provides the drug with stability and transdermal permeation properties. To achieve these goals, the formulation preferably contains several components as follows:

1) Non-aqueous solvent

LD and its derivatives are more stable in non-aqueous solution than in aqueous solution. A preferred solvent is propylene glycol which is non-toxic, does not produce skin irritation and provides the proper constituency for dermal application. Other non-aqueous solvents with similar properties may also be used for this purpose.

2) Transdermal enhancer and stabilizer

A preferred transdermal enhancer and stabilizer is carboxylic acid. The alkyl-esters of LD are quite soluble and much more stable in an acidic environment than in a neutral environment. The carboxylic acid also keeps the LD derivative uncharged and helps permeability through the skin.

3) Detergent

Detergents have been shown to be transdermal enhancers. The detergent should not interfere with the chemical stability of the penetrating drug and should not be toxic. We found that sodium laurylsulphate and sodium deoxycholate are adequate detergents for the purpose of transdermal delivery of LD. Yet, other detergents may also be appropriate for this purpose.

Reference is now made to Figs. 1 and 2 which illustrate apparatus 10 for transdermal administration of levodopa, constructed and operative in accordance with a preferred embodiment of the present invention.

Apparatus 10 preferably includes a storage compartment 12 which is in fluid communication with a dermal patch 14, preferably via a flexible plastic tube 16. Patch 14 may be made of any suitable material, such as cloth or plastic. Storage compartment 12 is preferably flexible and compressible by mechanical pressure. Storage compartment 12 preferably contains a fluid 18 (Fig. 2) which is a treating drug, such as an alkyl-ester of LD, dissolved in a formulation, such as described hereinabove in accordance with a preferred embodiment of the present invention.

In accordance with a preferred embodiment of the present invention, the alkyl-ester of LD is kept pre-weighed as a dried powder. Carbidopa (25 - 50 mg/tablet) is preferably ingested two hours before the beginning of the transdermal delivery of the LD derivative and then three times a day throughout the entire treatment. Preferably just before the beginning of the dermal application, the alkyl-ester of LD is placed in storage compartment 12 and a sufficient amount of formulation is added therein, and the constituents are thoroughly mixed together. Storage compartment 12 is then preferably tied to an arm or any other suitable location on a patient, such as with a strap 20, and connected to patch 14 via tube 16.

Flow of fluid 18 from storage compartment 12 to patch 14 is preferably controlled by a regulating valve 22. Patch 14 is preferably attached to the skin along an adhesive periphery 24, and a central portion 26 is preferably adapted to receive and maintain a quantity of fluid 18. Fluid 18 spreads under patch 14 preferably via a system of hollow capillaries 28 (Fig. 2), and penetrates the skin of a patient.

In a normal mode of application, fluid 18 flows from storage compartment 12 to patch 14 by gravity, or alternatively by a miniature pump (not shown). When necessary, flow of fluid 18 may be increased by exerting mechanical pressure on storage compartment 12 or by increasing the pump rate.

Apparatus 10 is preferably disposable. The location of apparatus 10 on the patient's skin may be changed periodically. Supplemental oral treatment may be given during the transdermal delivery according to clinical needs.

Various preparations of LD have been tested by the inventors and the experimental results are now presented.

Solubility of LDEE: The solubility of LD, LD methyl ester (LDME) and LD ethyl ester (LDEE) was examined in several potential solvents, with increasing amounts of the three LD derivatives being added to a constant volume of 5% propionic acid in water or 10% propionic acid in propylene glycol. We found that only negligible amounts of LD or LDME

were soluble in the two solvents, whereas at least 660 mg LDEE were soluble in 1 ml of both solvents. Adding 33% glycerol to the aqueous solvent did not significantly alter the solubility of the three derivatives, although a higher concentration of propionic acid (10%) was needed in the case of the aqueous solutions.

Stability of LDEE: The stability of LDEE was tested in several combinations of potential components of the formulation. For this purpose, 500 mg LDEE was dissolved in 1 ml 5% propionic acid just before the beginning of the stability experiment. In parallel, 500 mg LDEE was dissolved in 1 ml propylene glycol containing 10% propionic acid. These preparations of LDEE were used as stock solutions for several tested formulations as follows:

1) LDEE in aqueous solution of 5% propionic as prepared above.
2) Same solution as in No. 1 above + 5% sodium deoxycholate.
3) Same solution as in No. 1 above + 5% sodium dodecylsulfate.
4) Same solution as in No. 1 above + 5% Tween-20.
5) Same solution as in No. 1 above + 5% tritonX100.
6) Same solution as in No. 1 above + glycerol at a ratio of 1:1.
7) Same solution as in No. 1 above + propylene glycol at a ratio of 2:1.
8) LDEE in propylene glycol containing 10% propionic acid.
9) Same solution as in No. 8 above + 5% sodium deoxycholate.
10) Same solution as in No. 8 above + 5% sodium dodecylsulfate.

The above LDEE formulations were run on a thin layer chromatography (on silica gel - Merk Art. 5735; and on cellulose - Merk Art. 5574) for a qualitative detection of LDEE and its degradative products. The various LDEE formulations were kept at room temperature for several days and separation of the LDEE and its degradative products on the thin layer chromatography were repeated at various times after dissolving the LDEE. The running solvents for the thin layer chromatography were:

a) Propanol: Butanoic Acid: Water (20:4:10).
b) Dichloromethane: Acetone: Ethyl-Acetate: Methanol (35:15:1:0.25).

Immediately after the preparation, LDEE appeared on the thin layer chromatography as a single spot. No degradative products were seen at this stage. Degradative products appeared in formulations that contained tritonX100 24 h after dissolving the LDEE. Other formulations did not show significant degradation 24 h after dissolving the LDEE. At 48 h after dissolving the LDEE, degradative products appeared in all the aqueous solutions with the following order of degradation: formulation containing tritonX100 > formulation

containing Tween-20 > formulation containing sodium dodecylsulfate = formulation containing sodium deoxycholate. In the propylene glycol-based formulations, the LDEE was stable for more than 48 h.

Pharmacolanetic study: In a pilot experiment of transdermal delivery, two human volunteers were exposed for 24 h to LDEE dissolved in propylene glycol containing 10% propionic acid and 5% of either sodium deoxycholate (one volunteer) or sodium dodecylsulfate (one volunteer). Blood samples were taken at various times after the application of the LDEE on the skin and LDEE in the serum was separated on high performance liquid chromatography and determined with an electrochemical detector. The protocol and the details of this pilot study are described in the enclosed appendix. The results showed that blood levels of LDEE after dermal application using the above mentioned formulations could reach about 200 ng/ml. These levels are considered appropriate for obtaining therapeutic effect in Parkinson's patients.

It will be appreciated by persons skilled in the art that the present invention is not limited by what has been particularly shown and described hereinabove. Rather the scope of the present invention includes both combinations and subcombinations of the features described hereinabove as well as modifications and variations thereof which would occur to a person of skill in the art upon reading the foregoing description and which are not in the prior art.

CLAIMS

What is claimed is:

1. A pharmaceutical composition for treatment of Parkinson's disease comprising a compound of levodopa dissolved in a non-degradative solvent which allows transdermal administrtion of levodopa.

2. A pharmaceutical composition according to claim 1 and wherein said compound of levodopa is an alkyl-ester of levodopa and said solvent is a formulation comprising a substantially non-aqueous solvent, a transdermal enhancer and a detergent.

3. A pharmaceutical composition according to claim 2 wherein said alkyl-ester of levodopa is levodopa-ethyl-ester (LDEE).

4. A pharmaceutical composition according to claim 2 wherein said non-aqueous solvent has at least one of the following properties: non-toxic and non-irritant.

5. A pharmaceutical composition according to claim 2 wherein said non-aqueous solvent is propylene glycol.

6. A pharmaceutical composition according to claim 2 wherein said transdermal enhancer is also a stabilizer.

7. A pharmaceutical composition according to claim 2 wherein said transdermal enhancer is a carboxylic acid.

8. A pharmaceutical composition according to claim 7 wherein said carboxylic acid is selected from the group consisting of propionic acid and butanoic acid.

9. A pharmaceutical composition according to claim 2 wherein said detergent is selected from the group consisting of sodium laurylsulphate, sodium deoxycholate and their derivatives.

10. Apparatus for transdermal delivery of a substance for treatment of Parkinson's disease, said apparatus comprising:

a storage compartment containing therein a fluid for transdermal treatment of Parkinson's disease; and

a dermal patch in fluid communication with said storage compartment, said dermal patch being attached to a portion of skin of a patient, wherein said fluid flows from said storage compartment to said dermal patch and is thence transdermally delivered to said patient.

11. Apparatus according to claim 10 wherein said dermal patch comprises a plurality of hollow capillaries for flow of said fluid therethrough to the skin of said patient.

12. Apparatus according to either of claims 10 and 11 and wherein said storage compartment is compressible by mechanical pressure.

13. Apparatus according to any of claims 10 - 12 and comprising a regulating valve for controlling flow of said fluid from said storage compartment to said dermal patch.

14. A method for treatment of Parkinson's disease, comprising the step of transdermally administering a levodopa drug in a stable solution.

15. A method according to claim 14 wherein said step of transdermally administering said levodopa drug comprises substantially continuous transdermal penetration of levodopa.

16. A method according to claim 14 and wherein said levodopa drug comprises an alkyl-ester of levodopa.

17. A method according to claim 14 and wherein said solution comprises a substantially non-aqueous solvent, a transdermal enhancer and a detergent.

18. A method according to claim 14 and wherein said levodopa drug and said solution are stored separately and mixed just before transdermally applying said drug.

19. A method according to claim 14 and further comprising the step of ingesting carbidopa before commencing transdermal delivery of said levodopa drug.

20. A method according to claim 14 and further comprising the step of ingesting carbidopa during transdermal delivery of said levodopa drug.

21. A method according to claim 14 and further comprising the step of receiving an oral anti-parkinson's drug.

ABSTRACT

A pharmaceutical composition for treatment of Parkinson's disease comprising a compound of levodopa dissolved in a non-degradative solvent which allows transdermal administrtion of levodopa. The compound of levodopa is an alkyl-ester of levodopa and the solvent is a formulation comprising a substantially non-aqueous solvent, a transdermal enhancer and a detergent. The alkyl-ester of levodopa is preferably levodopa-ethyl-ester (LDEE).

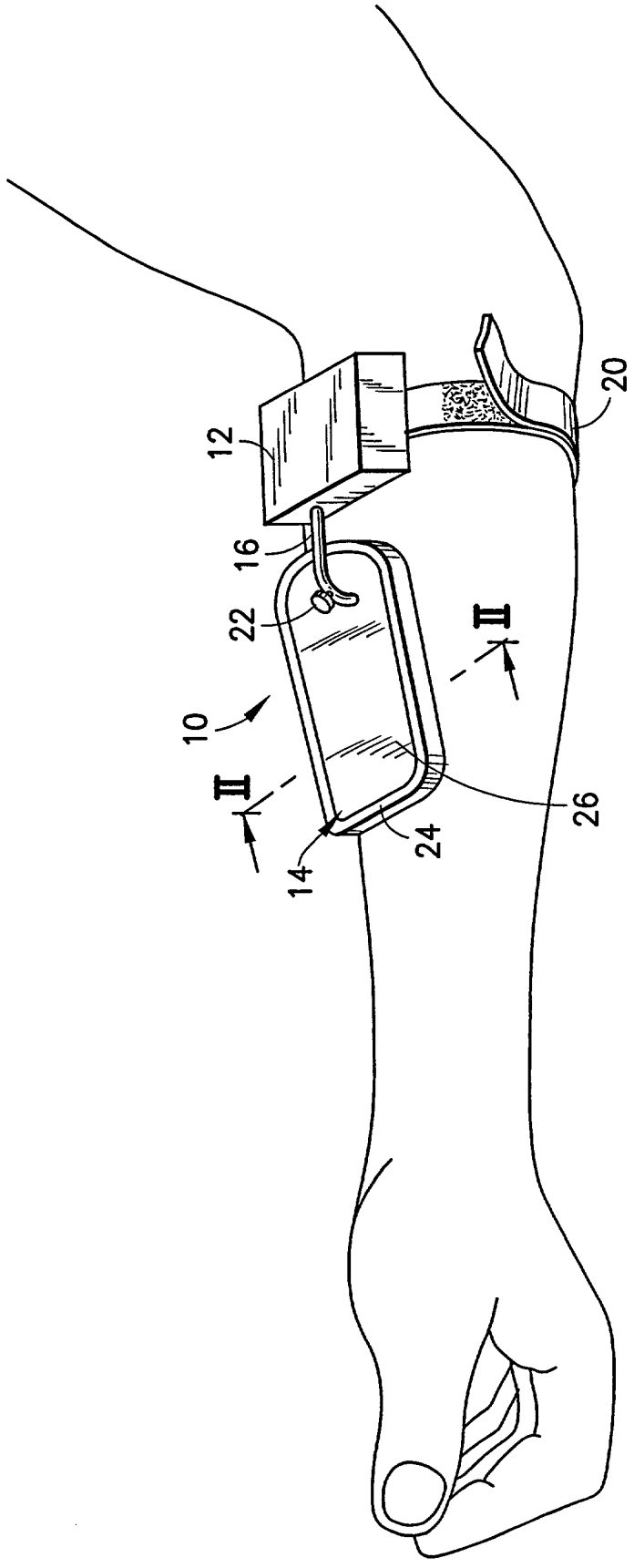


FIG.1

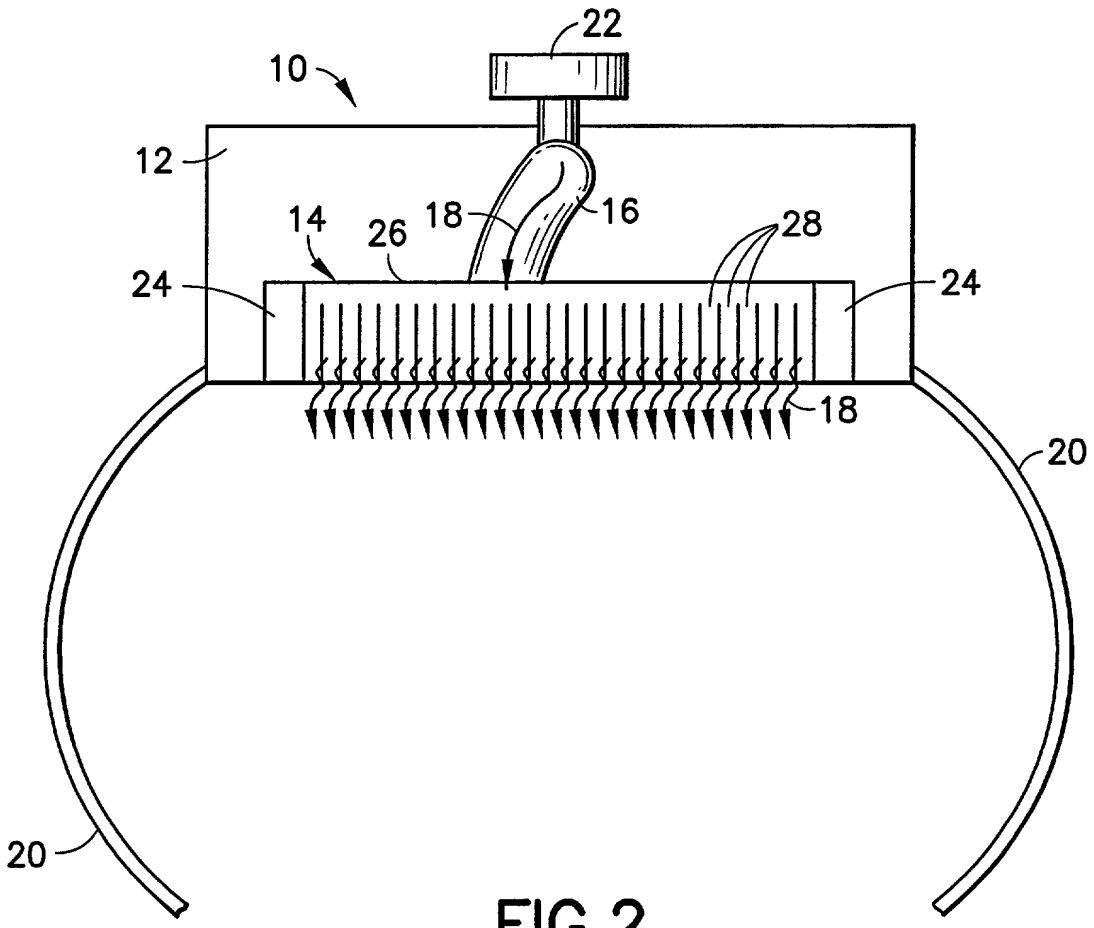


FIG.2

Docket No.
287985/002

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

TREATMENT OF PARKINSON'S DISEASE

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on **June 26, 1998** as United States Application No. or PCT International Application Number **09/287,951**

and was amended on **January 21, 2000 and April 7, 1999**

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
IL 119417	**Israel**	**10/13/1996**	☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

PCT/IL97/00327	10/09/1997	
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

Lawrence Rosenthal, Reg. No. 24,377
Steven B. Pokotilow, Reg. No. 26,405
Howard M. Gitten, Reg. No. 32,138
Matthew W. Siegal, Reg. No. 32,941
James J. DeCarlo, Reg. No. 36,120

Send Correspondence to: **STROOCK & STROOCK & LAVAN LLP**
180 Maiden Lane
New York, New York 10038

Direct Telephone Calls to: *(name and telephone number)*
(212) 806-5400

Full name of sole or first inventor **Moshe Kushnir**
Sole or first inventor's signature M. Kushnir Date 1/5/2000 (MAY 1st 2000)
Residence **Ramat Gan, Israel**
Citizenship **Israel**
Post Office Address **5 Jericho Street, Ramat Gan 52356, Israel**

Full name of second inventor, if any **Eliahu Heldman**
Second inventor's signature Eliahu Heldman Date June 5, 2000
Residence **Rehovot, Israel**
Citizenship **Israel**
Post Office Address **8 Simtat Hamuchtar, Rehovot 76516, Israel**